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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,746	09/29/2006	Ingmar Hoerr	067802-CU01-US1	9342

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
09/30/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,746	HOERR ET AL.	
	Examiner	Art Unit	
	MARIA MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/9/10*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-17 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7,9-17,21 and 27* is/are rejected.

7)☒ Claim(s) *2,3,8 and 22-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *replacement 2/9/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/8/11 has been entered. Claims 1-5, 7-17 and 21-27 are pending

Information Disclosure Statement

A replacement IDS filed 2/9/10 is submitted with this action providing a signature on each page of the 1449.

Claim Objections

Claims 1-17 are objected to because of the following informalities:

Claim 1 requires an article prior to "tumour" in line 2. Each of "a pathogen" and "a tumour" are individual limitations, the single article implies they are a combination in a single embodiment.

In claim 4, "the modulation of the immune response" lacks antecedent basis following the amendments. It would be proper to recite, --the stimulation of the immune response--.

In claim 9, the article "a" is required prior to "modified mRNA".

In claim 16, proper antecedent basis is provided by reciting in line 1, --at least one cationic or polycationic agent--. Similar amendment is required of claim 21.

Claim 17 states that the pathogen is an infection. However, more accurately, --the pathogen comprises a protozoan, a virus or a bacteria--. The use of and/or is confusing as it is not clear how a single pathogen can be more than one type. However, as amended, the scope allows for more than one item by use of the open language "comprising"

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 7, 17, 21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horton et al (US patent 7,268,120; see entire document) and Cannon and Weissman (DNA and Cell biology, 2002, pages 953-961; see entire document) in view of Kusakabe et al (J. Immunol 2000, Vol 164, pages 3102-3111). **This is a new rejection.**

Applicants claim a method for immunostimulation in a mammal by administration of at least one mRNA encoding at least one antigen of a tumor in combination with a GS-CMF mRNA wherein the GS-CMF mRNA is separately administered.

Horton et al each methods of delivery wherein a polynucleotide encoding a cytokine such as GM-CSF which induces an immune response (col 4, line 13-39) and in addition those encoding antigens such as bacterial and tumor (see e.g. col 23, line 35-59 and bridging ¶ col 47-

48). The polynucleotide is preferable an mRNA(see e.g. col 30, line 28-59). The polynucleotides can be complexed with histones (see e.g. bridging ¶ col 5-6).

> In one embodiment, the polynucleotide sequence encoding one or more cytokines is RNA. Most preferably, the RNA is messenger RNA (mRNA). Methods for introducing RNA sequences into mammalian cells is described in U.S. Pat. No. 5,580,859.

Towards this end, the art teaches that treatment protocols to produce immunity against pathogens and cancer function by inducing a cellular TH1 response. Towards this end, RNA vaccines offer many advantages (see e.g. Cannon and Weiss, abstract and page 955, col 1) and development of the TH1 response is accomplished by administration of GM-CSF after introduction of the vaccine. Kusakabe et al teach that immune activation by GM-CSF depends on the timing of administration of the cytokine. Administration of GM-CSF after administration of a vaccine induces a strong TH1 response.

Given these teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use cytokine mRNA in the treatment protocol of Horton et al because Horton et al teach that it is within the ordinary skill of the art to use tumor antigenic mRNA to modulate immune responses followed by GM-CSF mRNA administration and because Cannon and Weiss et al treat that mRNA administration is effective in inducing a TH1 response and Kusakabe et al teach that it is within the ordinary skill of the art to time GM-CSF administration to following tumor antigen treatment. In KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the

Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that mRNA vaccination methods are preferable in inducing TH1 responses and to this end GM-CSF after antigen administration is preferable. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horton et al (US 20050112141; see entire document) 1, 4, 5, 7, 17, 21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horton et al (US patent 7,268,120; see entire document) and Cannon and Weissman (DNA and Cell biology, 2002, pages 953-961; see entire document) in view of Horton et al (US patent 7,268,120; see entire document) further in view of Draghia-Akli et al (US 7,316,925; see entire document) or Weiner et al (US 20020123099; see entire document). **This is a new rejection.**

Applicants claim a method for immunostimulation in a mammal by administration of at least one mRNA encoding at least one antigen of a tumor in combination with i.e. a cytokine or CpG. The mRNA can be modified by increased GC content or increased AU content in the ribosome binding sequence.

The teachings of Horton et al are described above and are applied as before except the mRNA has not been modified by increased GC content or increased AU content in the ribosome binding sequence.

Cannon and Weisman actually teach that codon optimization is used with predictability to improve vaccines (see passage above).

Draghia-Akli et al teach that a bias of GC content can increase mRNA stability (see e.g. ¶ 0067).

Weiner et al teach that the environment of the ribosome binding site is improved by an AT rich sequence (see e.g. ¶ 0062).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to improve mRNA stability according to the methods of Draghia-Akli and Weiner et al for the methods taught by Horton et al because Horton et al teach that it is within the ordinary skill of the art to use tumor antigens mRNA to modulate immune responses and that stable mRNA is preferred and because Draghia-Akli and Weiner et al teach that it is within the ordinary skill of the art to alter nucleotide content to improve the stability. In KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that generation of increased stability of mRNA is done by known methods in the art. As well, it is within the ordinary skill of the art to use available methodologies to modify mRNA stability and one would have been motivated to do so in order as the ability do so by applying conventional methodologies. Based upon the teachings of the cited references, the high skill of one of ordinary

skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
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